

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Claims 1-17 were pending in the application and subject to a restriction requirement.

Claims 1-14 have been examined with respect to the elected SEQ ID NOS: 7-13, 18 and 19.

Claims 15-17 have been withdrawn.

Claims 1-5, 7-12 and 14 have been amended. Particular support for the amendment to claim 7 can be found on page 5, at line 15, of the specification. Support for all other amendments can be found throughout the specification with particular reference to the claims as originally filed. Claim 18 has been added, drawing support from throughout the specification and original claims.

No prohibited new matter has been introduced by way of the above amendments.

Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this Amendment.

Objection to the Specification

The specification has been objected to for allegedly lacking SEQ ID NOS identifying the sequences at the top of page 3. The objection is respectfully traversed. The examiner's attention is directed to the description of those sequences at the bottom of preceding page 2, where the 8 sequences at the top of page 3 are identified as SEQ ID NOS:1-8.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 2, 4 and 6-10 have been rejected under 35 U.S.C. § 112 as allegedly not being supported by a sufficiently enabling disclosure. The claims have been amended. To

the extent that the rejection might be applied to the claims as amended, the rejection is traversed.

Applicants respectfully submit that the rejection appears to be premised on a misconstruction of the claims as previously presented. In construing the breadth of the claims as the basis for an analysis of the *Wands* factors, the Examiner has alleged that the claims are written so broadly as to encompass all antibiotics, a very large genus of bacteria and an enormous genus of oligonucleotide sequences. OFFICE ACTION MAILED MARCH 20, 2007, at 4. In fact, the claims as previously presented, and as currently presented, recite that the claimed method is directed to testing *Streptococcus pneumoniae* for resistance to penicillin. Furthermore, claims 2, 4, 9 and 10 recite that the probes used in the method include probes consisting a discrete set of resistance-specific or sensitivity-specific oligonucleotide sequences. Thus, the analysis of the *Wands* factors presented in the Office Action does not correspond factually to the claims as previously presented or as currently presented.

Indeed, the Examiner has acknowledged that the specification is enabling for a method of identifying penicillin resistance in *Streptococcus pneumoniae* using probes selected from sequences recited in claims 2,4, 9 and 10. OFFICE ACTION MAILED MARCH 20, 2007, at 3. Consequently, the Examiner's analysis of the *Wands* factors alleged to be the basis for the rejection and the Examiner's conclusions based thereon are not directed to the claims that were, or are, of record. OFFICE ACTION MAILED MARCH 20, 2007, at 8.

Such a misdirected analysis of the factors for determining enablement cannot establish a *prima facie* case of non-enablement for the claims as presented. In the absence of reasoned allegations making out at least a *prima facie* case, applicants are under no burden to

make any further showing. Moreover, where as here, the alleged reasons for rejection do not reasonably correspond to the claims on record, it is impossible for applicants to respond.

The foregoing notwithstanding, applicants respectfully point out the following. The present specification teaches a relationship between the resistance to penicillin in *Streptococcus pneumoniae* and provides several example DNA probes for use in the claimed methods, including the species of probes to which examination has been restricted. On page 2, 3rd paragraph of the specification reference is made to Fig. 4 which shows a sequence alignment of the penicillin sensitive strain R6 with 30 representative penicillin resistant strains of *Streptococcus pneumoniae*. Fig. 4 clearly elucidates the pattern of mutations in penicillin resistant strains for a person of ordinary skill in the art. Thus, a skilled person can immediately take from Fig. 4 sequences that are specific for a penicillin sensitive strain, i.e., sequences of the R6 strains which correspond to regions of frequent mutations in penicillin resistant strains. A person of ordinary skill in the art could also discern which sequences are specific for penicillin resistant strains and which particular mutations are spread among various penicillin resistant strains. Figure 4 further elucidates which sequences are common to penicillin sensitive and penicillin resistant strains for a person of ordinary skill in the art. By reference to Figure 4, in conjunction with the teaching in the specification, a person of ordinary skill in the art can appreciate which residues may differ in a resistance-specific or sensitivity-specific probe. The claims recite a reasonable limit of up to four differences between the example sequences and other resistance-specific or sensitivity-specific probes.

Therefore, Figure 4 provides sufficient information to select suitable probes for use according to the method of the invention to discriminate between a penicillin sensitive and a penicillin resistant strain including the use of probes which differ by one to four nucleotides from SEQ ID NOS: 1-19. The sequences of targets of the probes are taught in Fig. 4 and it

would be only routine work without unpredictability for a skilled person to make a probe which hybridizes to a given sequence. Hence, the teaching of the specification is not limited to the representative examples of probes, but rather enables the skilled person without undue experimentation to make penicillin sensitivity-specific probes as well as penicillin resistant-specific probes for use according to the full scope of the claims as presented.

For at least the foregoing reasons, withdrawal of the rejection is appropriate and is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 2 and 4 have been rejected under 35 U.S.C. § 112 as allegedly not being supported by a sufficient written description. The claims have been amended. To the extent that the rejection might be applied to the claims as amended, the rejection is traversed.

The Examiner has alleged that the recitation of "sequences that differ by one to four nucleotides" encompasses a large genus of sequences that are not described in the specification. The statement of the alleged basis for the rejection does not account for significant facts regarding the description of the claimed methods in the specification. Therefore, the alleged basis of the rejection is not adequate to establish a *prima facie* case as required to support the rejection.

The use of probes differing from the exemplary sequences by one or several nucleotides, preferably up to 4 nucleotides, in the claimed methods is described in the last paragraph on page 4 of the specification. The entire set of sequences differing from the exemplified sequences by up to 4 nucleotides is an unambiguous set of sequences that is mathematically determinable by systematic alteration of the exemplary sequences by up to 4 nucleotides.

The sequences of PBP genes were known in the art. The specification discloses for each DNA probe of SEQ ID NOS: 1-19 the position of its target within the gene (see pages 3 and 4, 1st columns). Persons of ordinary skill in the art recognize that probes can contain a reasonable number of alterations while retaining a desired level of hybridization to target sequences. Considering the position of respective mutations within the target sequence, e.g., as shown in Fig. 4, a skilled person may replace one to four nucleotides of a sequence of SEQ ID NOS: 1-19, while retaining the original kind of specificity of the modified probe, i.e., penicillin sensitive or penicillin resistant. By disclosing which target sequence each of the probes of SEQ ID NOS: 1-19 relate to in the specification to a skilled person would be able to modify the given probes of SEQ ID NOS: 1-19 while maintaining their function, without need of further description.

Thus, the specification, with particular reference to Figure 4, describes a representative set of penicillin-sensitive and penicillin-resistant sequences so that a person of ordinary skill in the art would know which particular positions correspond to sensitivity or resistance to penicillin and which positions can be altered. Furthermore, a person of ordinary skill in the art would recognize that Figure 4 describes representative targets for sensitivity-specific and resistance-specific probes. A person of ordinary skill in the art would recognize that a description of a target sequence implicitly describes probe sequences that will hybridize to it, and would further appreciate that specific probes can differ from the complement of a particular target sequence to a certain degree and yet remain specific for the target sequence and implicitly recognize these variations by reference to the target and the knowledge available in the art.

Thus the specification provides more than ample description of the probes recited in the rejected claims for a person of ordinary skill in the art to appreciate that the inventors

were fully in possession of the claimed invention at the time the application was filed. The alleged basis for the rejection does not account for the forgoing facts and a prima facie case in support of the rejection cannot be made in view of the foregoing facts. Accordingly, withdrawal of the rejection is appropriate and is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph (definiteness)

Claims 1-14 have been rejected under 35 U.S.C. § 112 as allegedly being indefinite. The claims have been amended. To the extent that the rejection might be applied to the claims as amended, the rejection is traversed.

Claims 1-14 are alleged to be indefinite as a consequence of claim 1 reciting "sensitivity-specific DNA probes" and "resistance-specific DNA probes." Applicants note that claims 11-14 do not depend from claim 1. Applicants also respectfully submit that a person of ordinary skill in the art would understand the metes and bounds of the claims as previously presented when read in light of the specification. Nevertheless, applicants have adopted the phrasing suggested by the Examiner, which is not believed to change the scope of the claims. Corresponding amendments have been made of consistency of usage throughout the claims.

Claims 2 and 4 have been rejected, because it is allegedly unclear whether the probes consist of or comprise the recited SEQ ID NOS. Applicants respectfully submit that a person of ordinary skill in the art would understand the metes and bounds of the claims as previously presented when read in light of the specification, because the claims recited wherein the "probe is selected from ..." meaning that the probes have the recited sequences. The claims have been amended to recite that that "the DNA sequence of at least one DNA probe . . . consists of a DNA sequence selected from the group . . .

Claim 7 is alleged to be indefinite in reciting "stringent conditions." Applicants respectfully submit that a person of ordinary skill in the art would understand the metes and bounds of the claims as previously presented when read in light of the specification, because conditions for stringency are well understood. Nevertheless, the claim has been amended to recite that stringent hybridization occurs at 20° below the meting point of the hybridizing DNA.

For at least the foregoing reasons, withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1 and 6 have been rejected under 35 U.S.C. § 102 as allegedly anticipated by U.S. Patent Number 6,015,666 (Springer et al.). The rejection is traversed.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Springer et al. teach a method for detecting quinolone-resistant *Staphylococcus aureus*. Springer et al. teach a method comprising PCR amplifying with specific primers and then the detection of amplified DNA with what appear to be species-specific probes, but not resistance or sensitivity specific probes. The method taught by Springer et al. is therefore different from the claimed method. Springer et al. do not disclose detection of penicillin resistance in *S. pneumoniae*. Therefore, Springer et al. cannot anticipate the claimed invention.

Claims 1 and 6 are rejected under 35 U.S.C. § 102 as allegedly anticipated by Dowson et al. (*PNAS*, 87:5858-62, 1990). The rejection is traversed.

Dowson et al. describe an experiment to identify hypothetical transformants of two other *Streptococcus* species with the *S. pneumoniae* PBP2B gene. Dowson et al. do not disclose detection of penicillin resistance of *S. pneumoniae*. Resistance was already established in the tested bacteria. Therefore, Dowson et al. did not determine whether any *S. pneumoniae* was sensitive to penicillin as recited in claim 1. Consequently, Dowson et al. did not anticipate the presently claimed invention.

For at least the foregoing reasons, withdrawal of the rejections is appropriate and is requested.

Rejections under 35 U.S.C. § 103

Claims 2-4, 11, 12 and 14 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Dowson et al., *supra*, in view of Kell et al. (*Infection and Immunity*, 61:4382-91, 1993). The rejection is traversed.

The prior art fails to establish a proper *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143.

It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct applicant's invention from such prior art. *See, e.g., Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985); *see also, In re Shuman*, 150 U.S.P.Q. 54, 57 (C.C.P.A 1966). In asserting this rejection, the Office has taken a primary reference that is unequivocally directed to very distinct subject matter, and using impermissible hindsight attempted to reconstruct the presently claimed invention.

Dowson et al. describe an experiment to identify hypothetical transformants of two other *Streptococcus* species with the PBP2B gene. The method taught by Dowson et al. has a fundamentally different purpose and solves a different problem. Dowson et al. do not teach or suggest detection of penicillin resistance in *S. pneumoniae*. The probes disclosed by Dowson et al. were applied to DNA of *S. sanguis* and *S. oralis*.

Kell et al. do not overcome the shortcomings of Dowson et al. to arrive at the present invention. Neither, Dowson et al. nor Kell et al. provide any guidance on the selection of sensitivity specific or resistance specific probes from *S. pneumoniae*. Therefore, a skilled person could not combine the teachings of Dowson et al. and Kell et al. to arrive at the present invention. Nor would a skilled person be motivated to modify Dowson et al. to arrive at the present invention, because the problem solved from Dowson et al. is different from the problem solved by the present invention and modifying Dowson et al. in this matter would have defeated the purpose of the method of Dowson et al. It is well established that where modifying a reference would defeat the purpose or change the principle of operation, there can be no motivation to do so.

For at least the foregoing reasons, the prior art fails to establish a *prima facie* case of obviousness. Consequently, withdrawal of the rejection is appropriate and is requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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